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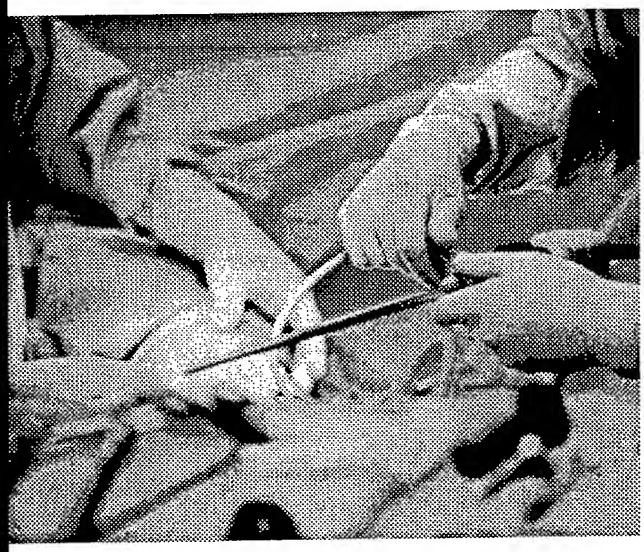

Biomaterials Availability

Potential Effects on Medical Innovation and Health Care

Science and Technology Policy Institute

IP-194

Science and Technology Policy Institute

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Issue Paper

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Biomaterials Availability
Potential Effects on Medical Innovation and Health Care

Science and Technology Policy Institute

Prepared at the Request of the

National Institutes of Health (NIH)
Technology Assessment Conference
on Improving Medical Implant Performance
Through Retrieval Information:
Challenges and Opportunitites

Science and Technology Policy Institute

Director's Foreword

This Analysis

The Science and Technology Policy Institute's legislative charter calls for it to consult widely with representatives from private industry and to incorporate information and perspectives derived from such consultations into its work for the White House Office of Science and Technology Policy (OSTP) and other government agencies, offices, and councils. One of the ways in which the S&T Policy Institute fulfills this charge is through a fellowship program conducted in conjunction with the American Association for the Advancement of Science (AAAS). In this program, the S&T Policy Institute hosts one or more research fellows each year as part of its core research effort. This program enables senior scientists and technology experts from private industry to spend a year with the Institute and to participate in S&T Policy Institute research.

As part of his fellowship, Dr. Ram Bhat began an analysis of how the current business and legal environment has affected scientific innovation, research, development, production, and use in patient care of medical devices that incorporate implantable materials. Selected staff from RAND have continued and extended that analysis under the auspices of the S&T Policy Institute's core research program.

At the request of the National Institutes of Health's Office of Medical Applications of Research, a RAND Issue Paper has been developed from this analysis to provide technical and historical background for the NIH Technology Assessment Conference on Improving Medical Implant Performance Through Retrieval Information: Challenges and Opportunities. RAND Issue Papers explore topics of interest to the policymaking community. Although Issue Papers are formally reviewed, authors have substantial latitude to express provocative views without doing full justice to other perspectives. They are intended to stimulate discussion.

The S&T Policy Institute

Originally created by Congress in 1991 as the Critical Technologies Institute and renamed in 1998, the Science and Technology Policy Institute is a federally

funded research and development center sponsored by the National Science Foundation and managed by RAND. The Institute's mission is to help improve public policy by conducting objective, independent research and analysis on policy issues that involve science and technology. To this end, the Institute

- supports the Office of Science and Technology Policy and other Executive Branch agencies, offices, and councils
- helps science and technology decisionmakers understand the likely consequences of their decisions and choose among alternative policies
- helps improve understanding in both the public and private sectors of the ways in which science and technology can better serve national objectives.

Science and Technology Policy Institute research focuses on problems of science and technology policy that involve multiple agencies. In carrying out its mission, the Institute consults broadly with representatives from private industry, institutions of higher education, and other nonprofit institutions.

Inquiries regarding the Science and Technology Policy Institute may be directed to the addresses below.

Bruce Don
Director
Science and Technology Policy Institute

Science and Technology Policy Institute
RAND
1333 H Street NW
Washington, DC 20005

Phone: (202) 296-5000 x5351
Web: http://www.rand.org/centers/stpi
Email: stpi@rand.org

Contents

Summary

Biomaterials provide components for many life-saving and life-enhancing medical devices, including implantable items such as heart valves, orthopedic prostheses, and intraocular lenses. U.S. firms produce more of such devices and hold more patents on them than firms from any other nation. However, manufacturers of these devices face a potential shortage of the biomaterials necessary to make them. Producers of biomaterials have in recent years cut off or restricted the supply of their products to the makers of implantable medical devices. The resulting uncertainty over the availability of commercial biomaterials, including "off-the-shelf" materials that are still used in other industrial applications, is likely to have a number of repercussions.

This exploratory analysis examines the circumstances surrounding the potential shortage of biomaterials and its likely ramifications. Specifically, the paper has three aims: (1) to describe the context and causes of biomaterials suppliers' decision to reduce their products' availability for medical applications; (2) to gauge, insofar as possible, the nature and extent of the shortage; and (3) to explore the effects of a shortage of biomaterials on medical-device availability for patients and on the research and development that leads to medical technology innovation.

The Issue Paper is based on an extensive review of the literature in the field—medical, business-related, and legal—as well as interviews with decisionmakers and scientists in the biomaterials and medical-device industries. It should be noted that much of the information about the availability of materials and the actions of biomaterials suppliers comes from those same interested parties. An independent verification has not been undertaken by RAND or others. However, we have attempted to ensure that we used the most reliable and verifiable sources from this community. We also note that with the passage and signing of the 1998 Biomaterials Access Assurance Act, the Congress and the President, who have very different views on product liability legislation, have agreed that such legislation was necessary in light of possible constraints on the availability of biomaterials.

The Causes of a Potential Shortage

In recent years, some medical devices that incorporate biomaterials have been at the center of extensive litigation. Users of some of these medical devices have taken legal action against manufacturers, claiming that defects in the products were responsible for injuring them. Some suppliers of biomaterials have been drawn into the legal process over their materials' role in the products in question.

The costs arising from this litigation have been a major factor leading many companies with core competency in biomaterials to reconsider their position as suppliers for medical applications. These firms have either cut off or sharply curtailed the availability of implantable biomaterials for the manufacture of medical devices. A number of factors have influenced this decision. Principal among them is the biomaterials suppliers' concern over exposure to litigation. Other factors are the small size of the implant materials market, adverse publicity associated with implants, and potential involvement with the Food and Drug Administration (FDA), which regulates implantable medical devices but does not currently regulate biomaterial components.

DuPont, Dow Corning, Dow Chemical, and 12 other domestic and foreign companies restricted the supply of materials for implantable medical-device applications. These companies' decisions followed in the wake of two different sets of litigation. One is related to the Proplast® TMJ (temporomandibular joint) implant made by Vitek, Inc., and the other to the silicone-gel breast implant made by Dow Corning (a joint venture that is co-owned by Dow Chemical and Corning, Inc).

The litigation from the defective TMJ implants was one of the reasons for Vitek's bankruptcy. DuPont, whose Teflon® PTFE (polytetrafluoroethylene) was used as a small component in the manufacture of the implants, became the defendant in numerous lawsuits. DuPont was found not liable in every case litigated to verdict, but at a cost estimated at several million dollars. This cost far outweighs annual revenues from sales, estimated to be only a few hundred thousand dollars. Breast-implant litigation, involving thousands of women, billions of dollars, and conflicting scientific claims, has prompted Dow Corning to seek Chapter 11 bankruptcy protection. The parent Dow Chemical has now been drawn into legal proceedings. In a recent case where it was the sole defendant, the company was held responsible for a $14.1 million award. Notably, both DuPont and Dow Chemical have claimed that they had no involvement in designing, developing, testing, manufacturing, marketing, or selling the respective implants.

Possible Consequences of a Biomaterials Shortage

Limitations on the availability of biomaterials for medical applications could have three effects.

1. Medical-device firms may have to stockpile materials, divert resources from product innovation and development to find and to qualify alternative suppliers, confine their operations to offshore sites, abandon manufacturing certain products, or exit from the business. The situation could affect an estimated 85 products, 30 surgical procedures, and approximately 7.4 million patients—some in a life-threatening way.

2. Academic and entrepreneurial institutions may not be able to advance their research on future diagnostic and therapeutic approaches involving technologies such as tissue engineering and cell therapy and transform them into viable products, because most of these efforts require the use of biomaterials. This shortage could potentially cause innovation in this field to stagnate and reduce prospects of significantly lowering the costs of some health care practices.

3. Implantable medical devices for patients may be less available. The affected products include implants such as heart valves and hydrocephalus shunts, orthopedic prostheses, and intraocular lenses. Furthermore, the supply issues extend beyond biomaterials to include electronic circuits, batteries, and other increasingly important components of implantable devices. All told, these consequences could have substantial adverse impacts on patient care and public health in the United States.

It appears unlikely that these issues can be resolved with full public benefit without the participation of all the stakeholders, including patients. This paper attempts to include relevant descriptions from all perspectives including those of three patient advocate organizations—those representing the TMJ implant patients, the breast implant patients, and the hydrocephalus implant patients.

Concluding Thoughts

Balancing the interests of the various parties in the biomaterials debate—injured patients, benefited patients, manufacturers, and researchers—and considering potential benefits and risks to future patients that may come from research (or the lack thereof) is complex. If the policy approach we use in striking this balance does not appropriately regard the interests of all parties, including

current and future patients who could benefit from implantable devices, the overall benefit to the public could be lessened.

Although we are not able to draw strong conclusions about whether a biomaterials shortage affects the welfare of current patients and constrains the prospects of future medical innovation, this analysis suggests that the benefits to current and future patients of even less-than-perfect uses of biomaterials are undervalued in current court proceedings.

Court cases, which by their nature settle disputes between only a few of the many parties involved, often cannot adequately take into account the overall benefits of biomaterials products. This analysis has shown that even though the applications of some biomaterials result in undesirable outcomes for some patients, there are positive benefits for other patients that may be even more beneficial to society. In the absence of other policy mechanisms besides the tort system, the opportunity to find the best balance of benefits for all the parties involved may be constrained.

In July 1998, Congress enacted the Biomaterials Access Assurance Act in response to this evolving situation. The act's intent was to ensure biomaterials access for device manufacturers and those who develop implantable devices. The act affords biomaterials suppliers some shelter from liability lawsuits if they simply act as suppliers of the raw biomaterial for medical devices and the material meets quality standards. Although our examination does not provide strong enough evidence to conclude that the availability of biomaterials has adversely affected patient care and future innovation, the information we have collected suggests that the issue is important. Given this, a careful, fact-based examination of the evolving situation and a careful assessment of whether the legislation is having its intended effect are both warranted.

Acknowledgments

Individuals who have made a significant contribution in writing this collaborative effort include Ram Bhat, the AAAS Fellow at the S&T Policy Institute for FY 1996 who authored the original draft of this analysis, and Richard Rettig, a senior health policy analyst at RAND who provided general oversight and guidance. Additionally, RAND colleagues Elisa Eiseman and Jerry Sollinger have made significant contributions to the paper through technical comments and editing.

This analysis has been made possible by inputs from a number of people from a range of institutions. The S&T Policy Institute is indebted to those listed below who have taken an active interest in the subject and provided significant comment on this effort. Mistakes, misinterpretations, and other oversights that have found their way into this paper are not their responsibility.

Academic Institutions
Robert Langer, Sc.D.
Pierre M. Galletti, M.D., Ph.D.
Jeffrey A. Hubbell, Ph.D.
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Robert C. Eberhart, Ph.D.
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Joachim Kohn, Ph.D.

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Kevin O'Connor
James Benson
Bernard Leibler, M.A.

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Richard A. Merrill, L.L.B.
Vincent Brannigan, Ph.D.

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Ross Schmucki
Katherine Knox
Stephanie Burns, Ph.D.
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John H. Lapke
John D. Paulson, Ph.D.

1. Introduction

Components for many life-saving and life-enhancing medical devices, including implantable items, such as heart valves, are composed of what are called biomaterials. Many of these materials are "off-the-shelf" materials which are used in other industrial applications. U.S. firms produce more implantable devices and hold more patents on them than firms from any other nation. Many of these firms are small and manufacture devices by integrating components or biomaterials obtained by supplier firms with different core competencies.

Manufacturers of many implantable medical devices face a potential shortage of necessary biomaterials because some producers have decided to cut off or restrict the sale of their products to the makers of implantable medical devices. A major reason cited for these decisions is the threat of legal action against materials suppliers for injuries associated with the devices. Furthermore, biomaterials have only a modest market.

Constraints on the availability of biomaterials for use in medical devices could have several undesirable consequences. They could make it difficult, costly, or even impossible to manufacture some currently available devices, thus threatening the health of patients who would benefit from them. Existing devices possibly in jeopardy because of the potential biomaterials shortage include implants such as heart valves, hydrocephalus shunts, orthopedic prostheses, and intraocular lenses. By one industry estimate, reduced biomaterials availability could adversely affect approximately 85 products, 30 surgical procedures, and 7.4 million patients.[1] Moreover, a biomaterials shortage could make it more difficult, costly, or even impossible for academic and entrepreneurial institutions that require biomaterials in their research and development activities to create new medical devices. In view of the potential to develop future therapies—e.g., tissue engineering and cell therapy—lost innovation in this area could have profound detrimental effects on the health of the public.

In July 1998, Congress enacted the Biomaterials Access Assurance Act. Its intent was ensuring biomaterials access for device manufacturers and those who

[1]Health Industry Manufacturers Association (HIMA) (1994a); Biomaterials Availability Coalition (1994a).

develop implantable devices. The act affords biomaterials suppliers some shelter from liability lawsuits if they merely supplied the raw biomaterial for medical devices and the material met quality standards. It is not yet known if this legislation will have the intended effect on the availability of biomaterials.

This issue paper examines the circumstances and likely effects of the potential shortage of biomaterials for medical applications. The paper has three aims: (1) to describe the context and causes of biomaterials suppliers' decision to reduce their products' availability for medical applications; (2) to gauge, insofar as possible, the nature and extent of the shortage; and (3) to explore effects of a shortage of biomaterials on medical-device availability for patients and on the research and development that leads to medical technology innovation.

The paper is organized as follows. Section 2 defines and describes biomaterials and discusses their current state of research and development. This section—although somewhat technical—provides essential context for the interrelationships between biomaterials suppliers and medical-device manufacturers, as well as the health stakes in the availability of materials for device manufacturers and materials and device developers. Section 3 describes two major episodes of litigation involving biomaterials: the Vitek TMJ (temporomandibular joint) device, and silicone-gel breast implants. These well-known episodes exemplify the potential costs to materials suppliers if devices made from their products become entangled in large-scale litigation—potential costs that appear to weigh heavily in the thinking of materials companies as they decide whether to make their products available for incorporation in implantable medical devices. Section 4 reviews what is known about the effects of such litigation on the availability of biomaterials for incorporation in medical devices. The analysis is based on a review and synthesis of medical, business-related, and legal literature as well as interviews with decisionmakers and scientists in the biomaterials and medical-device industries and experts. Section 5 considers the perspectives of patients. It explains the issues of concern to patients who benefit from implantable devices and those who suffer injuries associated with such devices. It also tries to take into account issues associated with future patients and the consequences (both positive and negative) of future innovations in biomaterials and medical implantation technology. Section 6 discusses the likely effects of a shortage on the availability of medical devices, the device industry, and related R&D. The paper concludes with a brief overview of alternative approaches to addressing the issue.

2. Current and Potential Biomaterials and Their Medical Uses

Biomaterials have been defined and classified in various ways.[2] According to one definition, a biomaterial is

> any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or a part of a system which treats, augments, or replaces any tissue, organ, or function of the body.[3]

In some instances, such as with metals, ceramics, and the like, the term "biomaterial" is a misnomer because the materials themselves are not biological. "Implantable materials"—suitable for successful clinical implantation—is a more appropriate term.[4] However, the word "biomaterial" is deeply ingrained in the literature and the policy debate and is therefore used here.

Biomaterials in use today include metals and alloys, ceramics, synthetic polymers, biologically derived substances, and composites. They are used to repair, restore, or replace damaged or diseased tissue; in artificial organs; in artificial tissues; or in prostheses.[5] Development of some of these materials has evolved from a combination of material science and engineering with tissue, cell, and molecular biology and clinical sciences. Many materials used in medical applications today were not designed and, in some instances, not manufactured specifically for medical use. For example, polytetrafluoroethylenes such as Teflon® have been successfully used in catheters or vascular grafts, and ceramics have been successfully used in orthopedic prostheses. Such adaptation of existing and readily available materials is not surprising given the lack of detailed understanding of the interaction of materials with tissues and surrounding fluids. It has been estimated that more than 95 percent of the materials used in medical devices are standard industrial materials, qualified for medical use by the device manufacturers and not by the original suppliers.[6]

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[2] Park (1995).

[3] NIH (1982).

[4] Schmucki (1996).

[5] Brady and Clauser (1995).

[6] K. O'Connor, AIMBE Executive Director, "Statement on Introduction of Biomaterials Bill," January, 1995. The qualification process involves extensive investigation of the interaction of the materials with tissues and surrounding fluids.

Although performance requirements for a biomaterial—factors such as mechanical or physical properties and amenability to fabrication—differ from application to application, the universal requirement is "biocompatibility." Though lacking a rigorous and widely accepted meaning,[7] *biocompatibility* may be functionally defined as the acceptance of the material by the surrounding tissues and fluids of the human body and by the body as a whole,[8] and the ability of the material to perform with an appropriate host response in a specific application.[9] Biocompatibility is more important for materials used for permanent implants such as heart valves and hydrocephalus shunts than those used in temporary devices such as peripheral catheters.

Biomaterials Currently in Use

The medical devices available today contain a wide variety of biomaterials that are used in a broad range of functions. Uses vary widely from the simple placement of a contact lens to transcutaneous insertion of a temporary peripheral catheter to surgical implantation of a heart valve. The duration and extent of contact of the biomaterial with body tissues and fluids vary accordingly. The choice of a particular biomaterial for a given application is generally based on several years of adaptation, research, development, and testing of a large number of substances derived from both synthetic routes and natural sources. In implant applications, attention is paid not only to bulk properties of the materials, but also to their surface, chemical, and physical properties, which dictate recognition of and response to the material by cells, enzymes, and other molecules through various immune system signaling processes. Knowledge of the effects of pertinent biomechanics on the performance of the biomaterial is also responsible for some of the advances made in recent years. The biomaterials in current use and reviewed here are products of such extensive scientific and technological learning and development.

Currently, five types of biomaterials are in common usage: polymers, composites, metals and alloys, ceramics, and biologic biomaterials. The following table summarizes some of the important aspects of these five types of materials. It characterizes their typical uses and advantages and provides some insights into the unique capabilities that are characteristic of each type.

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[7] Ratner (1995).

[8] Park (1995).

[9] Williams (1987).

	Typical Uses	Advantages	Uniqueness
Polymers	**Device components Catheters Sutures Heart valves Ocular implants**	**Tailorable properties Cost-effectiveness**	**Biodegradable Bioerodible Bioabsorbable Bioresorbable**
Composites	**Dental and orthopedic components**	**Strength and weight**	**Mechanical properties**
Metals and Alloys	**Joint, hip, and knee replacements Bone plates, screws, and pins**	**Strength and ductility**	**Electrical conductivity**
Ceramics	**Structural implants Coatings**	**Resistance to wear and corrosion**	**Compatibility with bone scavenging processes**
Biologic Materials	**Soft tissue augmentation Vascular grafts Membrane replacement Wound dressings**	**Complex function replacement**	**Symbiotic relationships with implant site including self-reconstitution**

Types and Uses of Current Biomaterials

The subsections below detail the major types of biomaterials and their uses and characteristics.

Polymers.[10] Because it is easy to tailor their properties and to work with them and because they are cost-effective and versatile, polymeric biomaterials have become indispensable as components of a wide variety of medical devices, ranging from simple disposables to long-dwelling implants. The most commonly used polymers include poly(vinyl chloride), polypropylene, poly(methyl methacrylate), polystyrene and its copolymers with acrylonitrile and butadiene, polyesters, polyamides or nylons, polyfluorocarbons, polyurethanes, natural and synthetic rubbers, silicone polymers, polyacetal, polysulfone, and polycarbonate. Their most important applications include dialysis device components, catheters, sutures, vascular grafts, heart valves, ocular implants, and orthopedic components. Some of these polymers lend themselves fairly well to surface

[10] Lee (1995); Chu (1995).

modifications; examples include heparin and hydrophilic coatings to address specific problems such as thrombus formation in vascular grafts and frictional wear of orthopedic components, respectively.

Biodegradable, bioerodible, bioabsorbable, or bioresorbable polymers form an important class of polymeric biomaterials. Their importance derives from two considerations: first, they do not elicit permanent chronic foreign-body reaction or provide a persistent nidus for microbial colonization because they degrade and are absorbed by the body in a short time; second, some of them permit regeneration of healthy tissues through their resorption with concomitant proliferation of specific cell types. The latter factor has significant implications in tissue engineering, a rapidly emerging field relevant to medical-device development.

The resorbable polymeric biomaterials of current commercial importance include linear aliphatic polyesters (poly-glycolide, lactide, caprolactone, hydroxybutyrate) and their copolymers (poly-[glycolide-lactide], [glycolide-caprolactone], [glycolide-trimethylene carbonate], [lactic acid-lysine], [lactide-urethane], [ester-amide]), polyanhydrides, poly(orthoesters), and inorganic polymers such as polyphosphazenes. The most successful uses of this class of biomaterials have been in wound-closure devices such as sutures (poly-glycolide, [glycolide-lactide], [ester-ether], [glycolide-trimethylene carbonate], and [glycolide-caprolactone]), and, to a small extent, in drug delivery devices (poly- anhydrides and [orthoesters]).

In classifying polymers, a clear distinction between "biodegradable" (or "bioerodible") and "bioabsorbable" (or "bioresorbable") must be made. The former materials decompose in the body leaving some fragments that do not necessarily leave the body entirely; they may, in some applications, elicit harmless host responses. The latter are completely metabolized and either resynthesized into proteins, for example, or eliminated from the body, as in the case of some aliphatic polyesters and polyamino acids.

Composites.[11] A composite biomaterial is a solid composed of two or more phase-separated components bonded together to be an integral structure. Morphologically, one component forms the continuous phase in which the other components are embedded as discontinuous inclusions in the shape of platelets, fibers, or particles. Commercial examples of current composite biomaterials include dental composites (acrylic polymer matrix with inclusions of inorganics

[11] Lakes (1995).

such as quartz, barium glass, and colloidal silica) and orthopedic components (high-density polyethylene matrix with inclusions of carbon fibers).

Metals and Alloys.[12] Most important in this class are stainless steel; cobalt-chromium alloy; and titanium, aluminum, and zinc and their alloys. Metals are primarily used in replacement devices for joints such as hips and knees; internal fixation devices such as bone-plates, screws, and pins for hard tissues; and stents for opening of blood vessels and urinary fluid tracks. Dental applications employ gold and its alloys and amalgams composed of mercury, silver, tin, copper, and zinc. Tantalum is used in special cases such as wire sutures in some plastic and neurosurgical applications. Alloys of platinum and other non-corrosive metals in that group have wide application in pacemakers as conducting leads and other components.

Ceramics.[13] Ceramics are refractory, polycrystalline compounds, usually inorganic, including silicates, metallic oxides, carbides, hydrides, sulfides and selenides. As biomaterials, they are usually referred to as bioceramics and classified into three categories: bio-inert or nonabsorbables, bio- or surface-reactives, and resorbables.

The *nonabsorbable bioceramics* are nontoxic, noncarcinogenic, nonallergenic, relatively noninflammatory, and biocompatible and resist corrosion and wear. They are therefore well suited as biomaterials. They include alumina, zirconia, silicon nitride, and carbon in specific form. They are primarily used for structural-support implants such as hips, and, to a smaller extent, other products such as ventilation tubes, heart valves, and drug delivery devices. Even though their mechanical or physical properties dictate their utility as support structures, chemical properties also play an important role. For example, bone scavenges atoms from ceramics, as it does from metals, by ionic, hydrolytic, and enzymatic dissolution and incorporates them in remodeling processes.

Surface-reactive bioceramics include Bioglass® and Ceravital® (mixtures of oxides of silicon, calcium, sodium, phosphorus and, additionally, magnesium and potassium for the latter), dense and nonporous glasses, and hydroxyapatite. They can form strong, but not permanent, bonds with surrounding tissues. An important application is in coating metal prostheses such as hips to enable tissue ingrowth and bonding for enhanced structural integrity. The bone scavenging process described above is of particular importance in such coating applications.

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[12] Park (1995).

[13] Bajpai and Billotte (1995).

Various other uses include dental and periodontal reconstruction, construction of bone plates and screws, and filling bone defects.

Resorbable bioceramics appear in implants that endogenous tissues gradually infiltrate as the implants degrade and are absorbed by the body. They consist of a variety of phosphates (calcium, tricalcium, aluminum-calcium, zinc sulfate-calcium), oxides (zinc-calcium-phosphorus, ferric-calcium-phosphorus), corals (mostly calcium carbonate), and Plaster of Paris (calcium sulfate dihydrate). Applications include repairing bone damage due to disease or trauma, filling bone defects at various body sites, and as local drug delivery devices.

Biologic Biomaterials.[14] This class consists of natural skin, arteries, veins, or other components that are used for grafting in place of excised diseased or defective tissues; blood-derived components such as fibrin and thrombin; tissue-derived substances or modified extracellular matrix components such as collagen, which is reconstituted and fabricated by itself or with compatible materials such as alginates; plant-derived substances such as cellulosics, which are reconstituted and subjected to such reactions such as oxidation; and certain other naturally derived materials including polysaccharides such as hyaluronic acid, chitin, and chitosan, and polyaminoacids such as poly-glutamic acid and lysine. Whereas most of these have specific, narrowly defined uses, collagen-based biomaterials cover a broad range of applications including fabrication of devices for hemostasis, injectables for soft tissue augmentation, vascular grafts, corneal shields, wound dressings, surgical sutures and membranes, and drug-delivery devices.

Trends in Biomaterials Research and Development

Several academic centers and small start-up companies are making substantial progress in numerous branches of biomaterial science, technology, and applications. Among them are implantable biosensors,[15] artificial muscle structures from conducting polymers[16] or shape-memory materials such as nickel-titanium alloys,[17] drug-delivery hydrogels from "intelligent" polymers,[18] wound dressings and antiadhesion products from bacterially synthesized

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[14] Li (1995).

[15] Borman (1996); Usmani and Akmal, eds. (1994).

[16] Yam (1995); Hunter (1995).

[17] Park (1995).

[18] Hoffman (1995); Tanaka et al. (1995).

cellulosics,[19] tissue sealants and adhesives and structures for tissue augmentation and regeneration from biotechnologically synthesized proteins,[20] cell and tissue encapsulation or immunoisolation devices using polymer membranes,[21] and highly specific surface modification of conventional materials using a host of advanced technologies[22] such as ion implantation, pulsed plasma polymerization, self-assembling monolayer formation, and chemical reaction to impart "biologically endowed" surfaces—most with realistic commercial potential.

One noteworthy recent trend in biomaterials is the rapid growth in tissue engineering activities.[23] These long-term, interdisciplinary research efforts place heavy demands on intellectual and financial resources and are often fraught with a great deal of uncertainty about the return on investment. Nonetheless, these attempts to create means to manipulate and reinstate tissue functions have important potential for expanding the realms of localized drug delivery, tissue transplantation, organ reconstruction, and cell and gene therapies. Patients in the United States who suffer tissue loss and end-stage organ failure undergo about 39 million medical procedures annually at a cost of about $400 billion.[24] There is hope that some inadequacies of prevailing therapies, such as donor shortage and limitations of mechanical devices, can be overcome by the products of tissue engineering. Optimism stems from the fact that tissue-engineered, transplantable skin constructs from several entrepreneurial companies[25] have shown clinically promising results in treating difficult wounds from burn injuries, pressure sores, and venous stasis and diabetic ulcers, and that similar progress has also occurred with bone and cartilage engineering. The potential importance of such advances is evident from the large number of annual procedures dealing with burns (2.15 million), pressure sores (1.5 million), ulcers (1.1 million), bone (1.3 million), and cartilage (1.1 million).[26] The skin, bone, and cartilage constructs have become the core activities of a few commercial ventures.[27] Efforts to form a wide variety of hybrid cellular scaffolds toward

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[19] Brown (1992, 1994).

[20] Capello (1992a, b); Cappello et al. (1990, 1994).

[21] Lanza and Chick (1996); Galletti et al. (1995a); Lacy (1995); Cytotherapeutics, Inc. (1993).

[22] "Update on Synthetic Biomaterials" (1996).

[23] Langer (1996); Palsson and Hubbell (1995); Galletti (1995b); Langer and Vacanti (1993); Hubbell and Langer (1993).

[24] Langer and Vacanti (1993).

[25] Examples of such companies are Integra LifeSciences, Organogenesis, Advanced Tissue Sciences, and Genzyme.

[26] Langer and Vacanti (1993).

[27] "Trends in Wound Healing and Tissue Engineering" (1995).

engineering of other vital organs (kidney, liver, nervous system) and skeletal muscle are at the forefront of research at several laboratories.[28] For treating cardiovascular disease, tissue engineering principles are applied to the development of autograft or xenograft heart valves or the reconstruction of heart valve leaflets from biodegradable or bioabsorbable polymer scaffolds and the patient's own cells.

Signifying the importance of these advances, a Tissue Engineering Working Group, approved in January 1995 by the National Heart, Lung and Blood Institute (NHLBI), strongly endorsed two NHLBI initiatives—one on "Tissue Engineering in Cardiovascular Implants" and the other on "Centers of Excellence in Cardiovascular Biomaterials."[29] Indicating an initial commercial interest in the potential of tissue engineering technologies, some companies, including venture firms and new public companies, are investing tens of millions of dollars for development of encapsulated cell implants—some with diabetes as the primary target and others aimed at the liver, kidney, and cornea.[30]

In sum, biomaterials components of medical devices are involved in treating diseases of a large number of organs (heart, lung, eye, ear, bone, kidney, and bladder) and systems (skeletal, muscular, circulatory, respiratory, integumentary, urinary, nervous, endocrine, and reproductive). This places a heavy burden on the biomaterials research and development community not only to work in newer fields such as tissue engineering and cell therapy, but also to improve understanding of host response to conventional biomaterials. Most of the $86 million NIH support for biomaterials was spent on such efforts, rather than on research into new biomaterials.[31] The extensiveness and importance of these developments are reported in the proceedings of several biomaterials-related group organizations.[32]

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[28] Service (1995); Palsson and Hubbell (1995).

[29] Anderson et al. (1995).

[30] "Developments in Organ Transplantation and Tissue Engineering," (1995).

[31] National Heart, Lung and Blood Institute (1995).

[32] These include the American Institute for Medical and Biological Engineering (AIMBE, 1200 G Street, N.W., Suite 500, Washington, D.C. 20005), Society for Biomaterials (6524 Waker Street, Suite 215, Minneapolis, MN 55426), Surfaces in Biomaterials Foundation (P.O. Box 26111, Minneapolis, MN 55426), Biomaterials Availability Coalition (P. O. Box 14293, Washington, D. C. 20044-4293), American Society for Artificial Internal Organs (ASAIO, P.O. Box C, Boca Raton, FL 33429), and a number of international professional societies in biomedical engineering. See Laxminarayan (1995).

3. Supplier Exit from the Market

In 1992, three major suppliers of biomaterials for medical applications—DuPont, Dow Chemical, and Dow Corning—announced that they would cease supplying their products to manufacturers of implantable medical devices. The companies attributed their decisions to various business and legal factors, including the high and unpredictable costs of litigation involving medical devices that incorporate biomaterials.[33] Other factors cited were the extremely small size of the implant market and concerns over adverse publicity associated with implants. Yet another concern voiced was possible future involvement with the FDA, although that agency currently does not directly regulate the separate components of implantable devices, only the devices themselves. Several other materials suppliers have followed suit.[34]

The decisions were preceded by two major litigation episodes that involved suppliers of biomaterials. The first was the legal action concerning the temporomandibular joint (TMJ) implant, manufactured by Vitek, Inc.; the second concerns litigation surrounding silicone-gel breast implants.

The Proplast® TMJ Implant Litigation

The Implant. Common treatments of temporomandibular joint (TMJ) disease include surgical implantation of an interpositional implant (IPI) or of prostheses replacing parts of the TMJ. The Proplast® TMJ Implant was designed, manufactured, and sold by the now-defunct Vitek, Inc., founded in 1969 by Dr. Charles Homsy, a former (1959–1966) DuPont scientist. The implant consisted of Vitek's Proplast®, a spongy biomaterial intended to encourage tissue ingrowth, and DuPont's slippery fluorinated ethylene propylene (FEP) film. It was constructed by laminating Proplast® with FEP, using a proprietary process that included sanding, heating, and compressing the film to fuse it to the Proplast®. The Proplast® in the implant was intended to anchor the implant to the upper bone of the TMJ (temporal) and the FEP film was intended to protect the Proplast® from the pressure caused by the lower part of the TMJ (condyle, the

[33] Schmucki (1995); Knox (1994).

[34] Aronoff Associates (1994), p 12.

upper end of the mandible) by acting as replacement for the disc (meniscus) that serves as a lubricating cushion between the two TMJ parts.

The Materials. Proplast® was invented (1976) by Dr. Homsy in the Prosthesis Research Laboratory of Methodist Hospital, Houston. Proplast® combines a number of ingredients including carbon and aluminum oxide fibers and salt with small amounts of DuPont's Teflon® polytetrafluoroethylene (PTFE) in a Vitek-patented eight-step process that includes solvent mixing, filtration, high-pressure compression, rolling, drying and high-temperature sintering, leaching, and re-drying. Although the process does not alter the PTFE molecule, the incorporation of other materials and the physical manipulation make the soft, spongy, absorbent and porous Proplast® substantially different from the hard, slippery, nonabsorbent and nonporous Teflon®.

FDA Approval and Early Results. Throughout the 1970s, Vitek conducted extensive animal and clinical studies on PTFE, FEP, and Proplast®. The studies included a five-year multicenter clinical trial involving 12 university hospitals and about 900 patients, and reported excellent results. Some of the studies pertained to the use of Proplast® in load-bearing applications.[35] By the late 1970s, Vitek had presented numerous reports on Proplast® to the FDA for approval of use in medical treatments, including the coating of metal TMJ implants. Three FDA expert panels, concluding that the safety and effectiveness of the material had been established through long-term clinical trials, conditionally recommended the approval of Proplast® for use as a Class II dental, ear, nose, and throat, and general plastic surgery device (1980–1982). The FDA subsequently accepted those recommendations (1987–1988).[36] In 1983, following the reports of about eight years of successful clinical results with the Proplast® TMJ Implant by Dr. John Kent, Chairman of the Department of Oral and Maxillofacial Surgery at Louisiana State University, and successful results from Vitek's own work, the company asked the FDA for and received permission to market the Proplast® TMJ Implant in the form of precut discs to match the natural geometry of the articulating surfaces of the TMJ. The device was subject only to "general controls" on the ground that the implant was "substantially equivalent" to a predicate device,[37] and that status was to continue until its classification into either Class II or Class III, at which time it would be subject to additional controls. Accordingly, Vitek began to sell the Proplast® TMJ Implant in 1983. At the 1984 American Association of Oral and Maxillofacial Surgeons

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[35] 47 Fed. Reg. 2810, 2818, January 19, 1982.

[36] 45 Fed. Reg. 86031, December 30, 1980; 47 Fed. Reg. 2810, 2818, January 19, 1982; Code of Federal Regulations 21 872.3960, 878.3500.

[37] FDA, Letter to Vitek, March 23, 1983.

(AAOMS) Clinical Congress, reference was made to 250 cases using "Proplast-Teflon" implants for disk repair or replacement with 93 percent success rate over a nine-year period.[38]

Problems and Withdrawal of the Product. At the 1986 AAOMS meeting, several surgeons reported catastrophic biomechanical failure of the implant, which caused a giant cell reaction leading to bone resorption and pain.[39] By 1988, Vitek had manufactured several thousand Proplast® TMJ Implants, each containing about 5 cents worth of DuPont's Teflon® PTFE. Approximately 4,000 patients appear to have received the implants. Eventually, these implants failed. Failure was due to many reasons, including the instability of the implants resulting from the anatomical complexity of the jaw and the magnitude of forces on TMJ. It has been reported that the FEP film failed to keep the Proplast® from breaking down and that the resultant fragments caused extensive injuries.[40] Details of the implant failure and its clinical consequences have been described in the literature.[41] In 1988, Vitek withdrew the Proplast® TMJ Implant from the market. In 1994, the FDA took all TMJ implants, regardless of composition and design, off the market and announced that "similar risks and similar safety and effectiveness concerns are associated with all TMJ implants."[42]

Litigation and the Results. The failures resulted in extensive litigation, which drove Vitek to bankruptcy in 1990. DuPont became involved in over 650 lawsuits filed by more than 1600 patients or their spouses in 42 states over eight years.[43] DuPont had not been held liable in any of the 53 cases decided by December 1995. These decisions have been reached on various grounds.[44]

Particularly noteworthy in this regard is the summary judgment granted in a multidistrict consolidated litigation involving 300 federal TMJ cases. Rejecting

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[38] AAOMS, *Criteria for TMJ Meniscus Surgery*, Section III, p. 15, November, 1984.

[39] Cowley (1994).

[40] *Jacobs v. E.I. Du Pont de Nemours & Co.*, 67 F.3d 1219 (6th Cir. 1995).

[41] Cowley (1994).

[42] 59 Fed. Reg. 65475, 65476, December 20, 1994.

[43] Schmucki (1995); Taylor (1995); The Wilkerson Group (1995), p 109.

[44] These included that DuPont's Teflon® PTFE and FEP are not defective or dangerous in and of themselves as sold by DuPont; that they are materials for multipurpose general industrial use and not designed or manufactured by DuPont for TMJ implant application; that Proplast® is substantially different from Teflon®; that there is no Teflon® TMJ implant; that DuPont did not endorse, design, make or sell the Proplast® TMJ Implant; that the bulk supplier/sophisticated user doctrine holds by virtue of the extensive knowledge and background of Dr. Homsy and Vitek with respect to the materials in question; that the materials supplier does not review or control the device manufacturer's package insert containing warnings and instructions in compliance with the FDA requirements; and that the supplier has no duty—nor is it appropriate—to provide warnings directly to the consumer (Schmucki, 1995).

the plaintiffs' claim that DuPont should be held liable because it acted as more than just an ordinary supplier of raw materials, the court's ruling stated that:

> To impose liability upon DuPont for the [multiple industrial] uses to which those [bulk supplied] products are put would force DuPont to retain experts in a huge variety of areas in order to determine the possible risks associated with each potential use. To require manufacturers of such "building block" materials to guarantee the safety of their products for each and every possible use would impose an unbearable burden on those manufacturers.[45]

Confining the responsibility to Vitek, the court added that "Based on [the] accomplishments by Dr. Homsy, the president of Vitek, reasonable minds could not differ as to the conclusion that Vitek was a 'sophisticated purchaser' as that term has been applied in this area of the law."

DuPont's Previous Materials Supply Policy. Since its expertise in materials science and technology did not extend to the medical implant field, DuPont adopted a conservative medical applications policy in the 1950s that required medical researchers and device manufacturers to agree to special terms and conditions of sale.[46] The policy stated that DuPont's materials were not made or endorsed for medical applications and included a disclaimer to the effect that the recipient, Vitek in the TMJ case, would perform all medical and other tests and obtain any necessary FDA approval. Thus, DuPont relied on the recipients to use its materials responsibly and the FDA to review the safety and efficacy of medical devices incorporating them.

Several noteworthy transactions in this regard pertain to the TMJ implant litigation.[47] Upon learning of Vitek's intent to use Teflon® for medical applications, DuPont advised Vitek, through policy statements, disclaimers, and conditions of sale, that its materials were not made for medical use and that Vitek would have to rely on its own judgment. DuPont also advised Dr. Homsy of the reports from the orthopedists John Charnley[48] and John Leidholt[49] about the problems of fragmentation and adverse reactions with PTFE in load-bearing prostheses, and references to these reports were later made in Dr. Homsy's own extensive writing.[50] Following the enactment of the 1976 Medical Device

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[45] "TMJ Implants Product Liability Litigation" (1995).

[46] Schmucki (1995); Knox (1994).

[47] *Jacobs v. E.I. DuPont de Nemours & Co.* (1995); *Hoyt v. Vitek, Inc.*, and *Morss v. Vitek, Inc.*, 134 Or. App. 271, 894 P.2d 1225, 1995.

[48] Charnley (1963).

[49] Leidholt and Gorman (1965).

[50] Homsy (1981).

Amendments, DuPont reiterated its policy, stating that Teflon® is made for industrial purpose only, that DuPont marketed no medical or surgical grades, that DuPont had not conducted any of its own testing on Teflon®'s efficacy in medical applications, and that DuPont conditioned the sale of Teflon® to those in the medical field on the user's assumption of responsibility.

DuPont's Current Policy. Even though DuPont had prevailed in all litigation at the time of writing, its costs from the TMJ implant litigation alone have been estimated at several million dollars, compared with the sales revenues of only few hundred thousand dollars. "Unpredictable and excessive costs of doing business with manufacturers of implantable medical devices" and a set of associated legal and business-related factors,[51] some have observed, led DuPont to restrict or terminate[52] sale of certain materials for use in implantable devices.

The Silicone Gel Breast Implant Litigation

The Setting. The events concerning breast implants are quite different from those surrounding the TMJ implants. Litigation over breast implants made by Dow Corning and other firms using silicone gel drove the company to seek protection under Chapter 11 bankruptcy and drew Dow Chemical into legal proceedings. Unlike the relation between Vitek and DuPont, where Vitek was an independent company in which DuPont had no management, ownership, or other interest, Dow Corning, formed in 1943, is a joint venture that is co-owned by Dow Chemical and Corning, Inc. Dow Corning was established to develop commercial applications for silicone. With regard to breast implants, the company played two roles: It was both the manufacturer of a device that it marketed itself and the supplier of material to other manufacturers of silicone gel breast implants.

Litigation. Even though Dow Chemical claimed that it never manufactured or tested silicone breast implants, attorneys for the breast implant participants argued that the company was as culpable for Dow Corning's missteps as Bristol-Myers, Baxter, and 3M were for the actions of the respective breast implant subsidiaries they once owned. Rejecting that argument on the grounds that Dow Corning was not a subsidiary of Dow Chemical but an independent company, a federal judge dismissed more than 3000 suits against the co-owners Dow Chemical and Corning in December 1993. Accordingly, Dow Chemical was not a participant in the February 1994 announcement of a $4.23 billion global

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[51] Knox (1994).

[52] DuPont (1993).

settlement between the plaintiffs' attorneys and the major breast implant manufacturers—$2 billion from Dow Corning and most of the rest from the other three major producers. However, this settlement never occurred because the funds were declared insufficient. Faced with the prospect of greater litigation, Dow Corning sought bankruptcy protection.

Persistent efforts by the plaintiffs' attorneys subsequently brought to light indications that Dow Chemical conducted human safety tests on silicone fluid under contract to Dow Corning from 1943 to the early 1970s, when Dow Corning set up its own toxicology laboratory; that Dow Chemical once controlled Gruppo Lepetit, a small company in Italy that marketed silicone breast implants outside the United States; and that Dow Chemical and Dow Corning jointly agreed to explore the possibility of developing silicone for pesticide and insecticide applications. Based on these observations, the federal judge in April 1995 reversed his earlier decision and reinstated Dow Chemical as a defendant in the breast implant litigation, stating that "under the substantive law of at least some states—though not necessarily all states—the evidence would create a jury question in federal court."[53]

Not waiting for this decision, a Texas state court judge concluded in the fall of 1994 that there was sufficient evidence to make Dow Chemical a defendant. In a Houston trial, which ended in February 1995, the verdict rendered by the jury held that Dow Chemical, by lending "substantial encouragement and assistance [to Dow Corning] in making the silicone breast implants using materials that had not first been adequately tested,"[54] was liable for 20 percent of a $5.2 million award to the patient for neurological damage suffered from leaking implants. Dow Corning, which had made the implant, was held responsible for the remaining 80 percent. However, the jury decision contained several inconsistencies. Subsequently, the judge reversed the verdict, stating that the jury's finding against Dow Chemical "will be disregarded as a matter of law" and held Dow Corning responsible for the entire $5.2 million award. [55]

The litigation from this matter has not yet been finalized. In a December 1999 federal court ruling in Detroit, women with silicone breast implants who voted against a $3.2 billion settlement plan will be allowed to sue Dow Corning's corporate parents, Dow Chemical Co. and Corning Inc., each of which owns half of Dow Corning. In a court-ordered vote among the Dow Corning implant recipients, 94 percent favored the bankruptcy plan, an unusually favorable

[53] Reisch (1995a).

[54] Reisch (1995a).

[55] Nocera (1995).

percentage in bankruptcy proceedings. As a result, fewer than 100 women are expected to pursue the individual lawsuits allowed under the plan. The settlement plan is part of a $4.5 billion bankruptcy reorganization plan for Dow Corning Corp. The ruling is expected to be appealed, and may reach the Supreme Court.[56]

Dow Chemical as a Sole Defendant. More recently, Dow Chemical was the sole defendant in a trial held in the Washoe District Court in Reno, Nevada. The plaintiff had originally sued Dow Corning along with Dow Chemical, and the court allowed her case against Dow Chemical to continue after Dow Corning filed for bankruptcy protection in May 1995 and the bankruptcy court stayed liability cases against Dow Corning. In October 1995, the jury concluded that the company acted with "conscious disregard" of the safety of the plaintiff, which led to debilitating autoimmune and neurological illnesses caused by her leaking breast implants. It awarded $4.2 million to the plaintiff and her husband in compensatory damages and then added $10 million in punitive damages. In December of 1998 the state's Supreme Court threw out the $10 million in punitive damages saying there was no evidence Dow Chemical tried to conceal defects, but it kept intact the award for compensatory damages. The court found that Dow Chemical had a duty to ensure the safety of Dow Corning's implants.[57]

Dow Corning's and Dow Chemical's Current Materials Supply Policies. Prompted by this litigation, both Dow Corning and Dow Chemical adopted policies to restrict or terminate specific materials for use in specific medical-device applications. On April 1, 1992, Dow Chemical (Dow Plastics) ceased selling its medical-grade resin and film products for use in cardiac prosthetic devices and all other long-term implants (30 days or more for Pellethane® polyurethane elastomer, 72 hours or more for other materials). On April 30, 1995, the firm stopped selling Pellethane® to existing customers for pacemaker applications.

Before declaring bankruptcy, Dow Corning also stopped sales of some products. As of March 31, 1993, it discontinued sale of several polysiloxane (silicone) products[58] for use in permanent implants (30 days or more), for drug-filled and load-bearing implants, and "for any applications related to reproduction, contraception, obstetrics, and cosmetic surgery and procedures." The policy allowed continued supply for short-term use, except in the six product categories

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[56] "U.S. Judge's Decision Could Complicate Dow Corning Breast-Implant Settlement" (1999).

[57] Bates (1999).

[58] SILASTIC® MDX4-4515/4516 and Q7-2245 Implant Grade Elastomers, SILASTIC® HP Tubing, all SILASTIC® Implant/Medical Grade Sheeting, Dow Corning Q7-2213 Dispersion.

(see footnote 58) and for a limited number of life-saving, long-term implant applications such as pacemakers, but only under very strict indemnification contracts.

These two lawsuits both involve commodity materials produced for other industrial uses besides implantable devices. The suppliers are large chemical companies with well-established materials research and development infrastructure. These materials are used as biomaterials in medical devices manufactured by small companies—similar to most in the country—strictly through adaptation and not by original design and development. The cases, particularly DuPont's problems with Vitek, have been cited as shaping the perspective of those biomaterials suppliers who have decided to withdraw from the market.[59]

Biomaterials suppliers are not insensitive to the societal value of the use of their materials in products that enhance or save lives. But if they perceive that the economic risk from this small part of their overall business is too great, it will outweigh other considerations in their decisions. This poses a dilemma: Choices that prevent undesirable uses of biomaterials may also preclude desirable uses. In the absence of other policy mechanisms besides the tort system, the opportunity to find the best balance of benefits for all the parties involved may be constrained because of the limited options the situation presents.

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[59] Baker (1995).

4. The Nature, Causes, and Potential Scope of a Biomaterials Shortage

From the perspective of the materials suppliers the situations described in the previous section imply the following:

- Medical implants can cause patients serious injury.
- The materials supplier can be brought into lawsuits resulting from injuries to patients from medical devices, especially when the device manufacturer declares bankruptcy.
- The potential liability associated with litigation is viewed by the materials suppliers to be out of proportion to the role that the material plays as a component of the implant or the size of the suppliers' business with the medical-device manufacturers.
- Even if found not liable, a supplier might still face substantial legal costs as well as other undesirable consequences, such as a tarnished reputation and management and staff diverted from the primary pursuit of the business.

Suppliers are likely to factor the last three consequences into any decision to sell material to a device manufacturer. They might be reluctant to risk expensive litigation by conducting such sales. This reluctance is even more likely if the product profits are low relative to other products or if they represent a small fraction of overall firm revenues and the risk in terms of potential damage to the firm is high. Thus, it is possible that suppliers might refuse to sell, and a biomaterials shortage could occur.

However, aside from the suppliers' public announcements and studies reviewed above, there is little empirical evidence about the potential shortage of biomaterials for medical-device manufacture. This may reflect a reluctance by publicly traded companies to acknowledge to stockholders the existence of a shortage of critical inputs. To gain more insight into the possibility and magnitude of such a shortage and to try to gauge its likely effects, we consulted a variety of sources. These included the literature and interviews with a cross-section of people from the industry, academia, consumer agencies, and the legal

profession.[60] Drawing on these sources, we have attempted to determine what suppliers have done, why, and the likely effects of their actions.

What Suppliers Have Done

The potential shortage of biomaterials results from the decisions by the major chemical and materials manufacturers to restrict or discontinue the supply of biomaterials currently used in permanent and short-term implantable medical devices such as blood vessel grafts, heart valves, stents, tissue or organ patches, catheters, ports, and orthopedic components. Dow and Dow Corning's actions are described in the previous section. Summarized here are the decisions of DuPont and some other industry suppliers.[61]

On January 15, 1993, DuPont began phasing out sale of material for use in "medical articles intended for permanent implantation in the human body or in permanent contact with internal body fluids or tissues." The process was completed by January 31, 1994. (Exceptions to this rule were limited to situations in which DuPont itself was involved in the design of the medical article, such as the DePuy-DuPont Orthopedics venture, or where business risk management strategies were adequate to justify a supplier-customer relationship.) In a letter to its customers, the company attributed its decision to the fact that "unpredictable and excessive costs of doing business with manufacturers of implantable medical devices no longer justifies unrestricted sale of standard raw materials to such manufacturers at customary prices." The company explained its action through its "DuPont Policy Regarding Medical Applications of DuPont Materials" and "Caution" statements. Both DuPont and Dow Corning sent letters to their customers explaining their decisions.[62]

Similar decisions have been made by other materials suppliers. Recently, a prominent U.S. producer made a business decision to stop making ultra-high-molecular-weight polyethylene (UHMWPE) available to the orthopedic product industry.[63] UHMWPE is currently a key ingredient in fabrication of hip and knee prostheses. These decisions to withdraw from the market have not induced other suppliers to enter it. Twelve domestic and foreign companies with core

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[60] See list of discussants appended to the paper.

[61] HIMA (1994); Aronoff Associates (1994); Biomaterial Availability Coalition (1994); Gould et al. (1993).

[62] DuPont (1993); Dow Corning (1992, 1993).

[63] Galletti, P., in a November 8 letter to Hon. Newt Gingrich, referred to in "Biomaterial Industry Presses Gingrich to Pass Product Liability Bill" (1995).

competency in materials have expressed no interest in supplying materials for implantable medical-device applications.[64]

Other Indications of Industry Reactions

The only study of this situation is one by Aronoff Associates,[65] commissioned by the Health Industries Manufacturers Association (HIMA), which presents the perspective of the materials suppliers, analyzes the reasons for their decisions, and assesses the potential impact of these decisions. The study was limited to the situation with PTFE, polyester fiber or yarn, and polyacetal resin. The findings, summarized below, identify the major factors affecting suppliers' decisions to withhold material.

- The most important factor from the material supplier's perspective in deciding whether to sell materials for use in implant products was the fear of exposure to costly, possibly catastrophic litigation.
- The second most important factor was that the small size of the market did not justify the risk. The combined size of the permanent medical implant market for the three materials in question is minuscule ($600,000) compared with the other markets, such as automotive and textile industries, for the same materials ($10.5 billion).
- Other reasons included dependence on precursor materials, fear of adverse publicity associated with implants, fear of involvement with the FDA, demand for nonstandard materials for very small volume products and presumption of the need for specialized production facilities.
- Most suppliers would be willing to provide materials only under the protection of stringent indemnification agreements.
- A major motivation for supplying appears to stem as much from a sense of social responsibility and humanitarian intentions as from economic considerations.

Such decisions affecting biomaterials availability have been characterized as the results of a system failure.[66] Although these decisions have resulted in suppliers withdrawing from the market, which has had a detrimental impact on some

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[64] Aronoff Associates (1994).

[65] Aronoff Associates (1994).

[66] J. H. Fielder, at American Institute of Medical and Biological Engineering (AIMBE)/AAAS Meeting (1995).

patients, we cannot say unambiguously that the situation has resulted in a lesser overall benefit to the public. This is because there is a complex relationship between such withdrawals and the overall benefits to society. It is not clear from either the data at hand or the law and economics literature that supplier withdrawal necessarily means that such decisions by the tort system are suboptimal for society.

This literature has developed a rich assessment of the ability and limitations of the courts to determine liability in the way that most greatly benefits society. To carefully assess whether or not a court decision is optimal we need to understand a broad range of issues. Some chief determinants include whether it is best for the industry to try to incorporate safety features before or after product introduction; others are whether or not products should rely on proven technology with lesser current benefits and risk, or rely on newer technology with greater benefits and risk.[67] Additional factors include whether or not bankruptcy by firms like device manufacturers is possible, or even likely, as a result of the court's ruling.[68] Understanding these factors and whether a particular court decision was based on a liability rule that used hindsight or relied on what was known when the product was designed, would allow some rough assessments. This would give some insights as to whether any particular decision took appropriate account of the current and future benefits to injured patients and as well as those to patients benefited by other uses of biomaterials that might be affected. Such an analysis is both beyond the resources of the current analysis and not needed for the more basic point we wish to establish.

The point is that courts, by the nature of the cases brought before them, must consider the damages suffered by the plaintiffs in those cases and evaluate the responsibility and liability of the parties involved. Because of the complexity of the situation outlined above, it is unlikely that the courts always have complete and correct information about all the patients who may be significantly affected by their judgments. This is particularly true if suppliers other than those involved in the case leave the market as a result of the court's decision.

We advance the hypothesis that the tort system may not adequately value the overall benefits to the public of biomaterials use. This is because a court may not adequately appreciate the broad impact its decisions could have on other patients, as we shall discuss in the next section. This possibility, combined with the broad and important uses of biomaterials outlined in the first section, argues

[67] Ben-Shahar (1999).

[68] Watabe (1999); van't Veld (1997).

that this matter calls for continued attention by policymakers beyond those concerned with the courts.

5. Patients' Perspectives on a Biomaterials Shortage

The lawsuits over implantable devices generally attract considerable publicity and media attention. Litigants often argue that device manufacturers and their associates have not made their most conscientious effort to reduce risk to the lowest possible level. The manufacturers, pointing to the limit of existing knowledge on the human body's long-term interaction with implants, counter that flawless performance is unreasonable and that the course of redress is often motivated by the defendant's solvency and ability to pay damages rather than by culpability.

This focus on litigation overshadows what is arguably the most important element, the patients themselves. Patients' perspectives vary widely. In some cases, they are people who suffer chronic, or permanent injury, and who feel that they have been victimized by inadequate testing of products. In other cases, they have local complications and possibly a long-term systemic disease. They are particularly bitter because known problems with implants or materials were, in their view, inadequately considered in the development and approval process. However, there are also those who stand to suffer greatly and perhaps die if the biomaterials controversy results in withdrawal of the only material that can serve their particular need.

A number of patient-assistance organizations have been formed to help patients who have suffered device-related injuries. Two groups—The TMJ Association, Ltd.,[69] and the National Breast Implant Task Force[70] and its affiliates—have been formed to assist those involved in the cases discussed above. Other patient representative groups exist, such as the Hydrocephalus Research Foundation, whose mission to help patients with respect to debilitating or life-threatening diseases cannot be fulfilled without the acceptance of responsibility by the scientific, regulatory, and legal communities. The following three examples present the widely different perspectives drawn from the experiences of these organizations, which must be considered in pursuing logical solutions to the problem.

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[69] 6418 W. Washington Blvd., Milwaukee, WI 53213.

[70] P.O. Box 21051, West Palm Beach, Florida, 33421.

TMJ Implants

The following summarizes a presentation by The TMJ Association, Ltd.,[71] that provides a comprehensive description of the problems related to the TMJ implants from a patient perspective.

The Disease and Its Prominence. The TMJs are the two tiny joints in the front of the ears that attach the lower jaw (mandible) to the skull (fossa). Clinical conditions usually classified as TMJ disorder include those with pain or dysfunction in the joint or contiguous structures. TMJ disorders affect approximately 30 million people, most of whom are women. The etiology and treatment of the disease do not seem to be well established because of a lack of well-funded research. The pertinent professional societies—the American Dental Association (ADA) and the American Association of Oral and Maxillofacial Surgeons (AAOMS)—have not made TMJ disease a specialty. At the National Institute of Dental Research (NIDR), the disease falls under the jurisdiction of the Craniofacial Anomalies, Pain Control, and Behavioral Research Branch, where it has not been a high priority. The Musculoskeletal Branch of the National Arthritis and Musclo-Skeletal Disease Institute and the Office of Research on Women's Health have shown interest in and commitment toward solving the problems related to the disease and its treatment. Continual efforts by the TMJ Association have prompted Congress to encourage the NIDR to collaborate with the other pertinent NIH institutes.

TMJ Implants and Their Failures. Common treatments of TMJ disease include surgical implantation of an interpositional implant (IPI) or of prostheses replacing parts of the TMJ (condyle, fossa, or both). About 150,000 patients in the United States are estimated to have received the implants. Most of the biomaterials used in these products were introduced before the 1976 Medical Device Amendments, and those marketed after 1976 relied on the "substantially equivalent" 510(K) categorization to obtain the FDA approval without adequate testing. A 510(K) application is based on the decision that a new device is the substantial equivalent of a previously approved device. Testing, therefore, is less than that required for a Pre-Market Approval application.

The two most widely used IPIs were Dow Corning's SILASTIC® and Vitek's Proplast® TMJ Implants. The former apparently produced good results in the short term, but within a few years of implantation, "fragmentation, perforation and deterioration of the material" and ensuing health problems such as arthritis

[71]Cowley (1994).

and lymph node swelling were reported. Dow Corning was alleged to have conducted no long-term animal or human studies before market introduction and to have known that SILASTIC® and the implant were unstable and that they caused adverse reactions. The inappropriateness of SILASTIC® for long-term implant use and the withdrawal of the implant in 1993 was determined only after 20 years of use. The problems with the Vitek Proplast® TMJ Implant have been described earlier in this paper. As with the SILASTIC® implant, the Proplast® implant also showed promising early results, only to fail and cause severe problems subsequently.

Patients' Experiences and Opinions. Many TMJ implant recipients are in their twenties or thirties. Through their experiences, the patients have educated themselves about implant failure, fragmentation, particle migration, the ensuing tissue reactions, and the craniofacial and systemic problems. Severity of injury has ranged from deformity and masticatory dysfunction to the degeneration of the fossa to the extent of perforation of the dura or the skull and the regression of the condyle to the extent of collapsing the throat. Some patients have undergone several post-removal procedures, as many as 43 surgeries in one case. In general, the patients report diminished quality of life due to health problems ranging from lingering discomfort and intractably chronic pain to numerous complicated symptoms. While some implant recipients are affected only by the anxious anticipation of the impending implant failure and the ensuing complications, the plight of the advanced patient continues in the absence of palliative or restorative treatments. Equally important are the psychosocial and financial impact of the problems on the patients and their families. There are reports of broken marriages, torn families, lost careers, and bankruptcy—which, combined with the physical problems, may have been ultimately responsible for over 50 suicides.[72]

Embittered patients feel abandoned by all the relevant factions. They hold the materials suppliers and the device industry responsible for introducing inadequately tested products; the surgeons and the health professionals' societies for not informing patients adequately about the risks and for not taking their ailments seriously; the governmental agencies for deficiencies in classifying the device, tracking the complaints, instituting the corrective measures, and failing to conduct basic research on the disease; and the health care system as a whole for failure to establish cooperation between its parts and the patients. Medwatch, a Medical Products Reporting System introduced by the FDA in 1993 for voluntary professional reporting of adverse events and product defects, has not served its

[72] Cowley (1994).

purpose well. The TMJ International Implant Registry, established by Medic Alert at the request from the FDA three years ago, has closed. These failures are taken as a consequence of the close ties between the device manufacturers and the surgeons who do not believe the patients when they complain. Patients comment that the TMJ implant materials are "marked by a pattern of haphazard development, entrepreneurialism, unverified assertions in the absence of animal testing and a silent FDA" and conclude that "if all the energy expended on damage control, denial and excuses went into a concerted effort to help the patients, all would be better off."[73]

With reference to the legal environment, patients share the general opinions of consumer advocates: that "virtually without exception, lawsuits the industry describes as frivolous turn out to be valid"; that "litigation is an inevitable result of misguided federal laws and policies that have allowed most medical implants to reach the public without extensive testing and specific approval by the FDA"; that "liability provides an irreplaceable incentive in making medical devices safer and in ensuring that consumers who are injured by defective devices are compensated"; and that "product liability actions are almost the consumer's only protection from dangerous, defective medical devices" in contrast to the bankruptcy provision available to the erring manufacturers. Emphasizing that a person receives an implant not with the intention of suing a company years down the road for financial gains but only in pursuit of relief from the disease, patients note that litigation may yield much for some, but many receive little and must undergo an emotional ordeal most sick people cannot bear.[74]

The patients' experiences have brought them unprecedented awareness of the surgeon, the procedure, the materials, the device, the manufacturer, the complications, the expected life span of the device, and such details. Patients are an inherent part of the implant venture because they take just as much risk as the device manufacturers and surgeons—or more, since it is the quality of their lives that is at stake. Stressing this interdependence, the patients appeal to the professionals to work with them on the best possible TMJ prosthesis.

Toward that end, they make several recommendations: that the FDA systematically solicit advice from the relevant agencies with expertise in materials and design; that the FDA develop a user friendly, multitrack complaint registry for the earliest possible warning signs; that an international implant retrieval and database system be established independent of the FDA to enable

[73] Cowley (1994).

[74] Cowley (1994).

identification of factors responsible for the success or the failure of the implants; that the development of the device become an integrated process involving component suppliers and the device makers sharing responsibility and accountability; that a TMJ device development team be established at the NIH to ensure integration of all the necessary knowledge; that there be a mechanism to ensure that the patient receives exactly the same device as promised; and that an international entity be established to address ethical issues arising from device and materials problems.[75]

Breast Implants

The patient perspectives on the problems associated with the breast implants are perhaps best described in a briefing paper authored by the American Trial Lawyers' Association (ATLA) Breast Implant Litigation Group (BILG).[76] The paper is supported by industry documents, testimony, and publications. It is not known with certainty if the paper represents the perspectives of all or a vast majority of the patients, but the views are endorsed by the National Breast Implant Task Force and its affiliates. The following summarizes the contents of the paper.

Inadequate Testing. Manufacturers have not tested the breast implants adequately for safety in accordance with the standards set by the scientific community and required by the FDA for use in humans.

Silicone Gel/Liquid. Early work on silicone gel/liquid injection and implants had given indications of bleeding or low molecular weight or extractable components from the implants and migration into major internal organs including spleen, heart, liver, lungs, and brain. The associated complications included atypical immune disease which came to be termed as "human adjuvant disease." The results of animal studies concurred, showing that silicone injections led to widespread dispersion of the material throughout the reticuloendothelial system with finding of abnormal vacuoles in the blood and the presence of the material in the various parts of the body. The FDA ruled that liquid silicone injections were to be limited to carefully controlled clinical settings and that under no circumstances should liquid silicones be used for injections in the breast because of the highly vascularized nature of the breast.

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[75] Cowley (1994).

[76] ATLA Breast Implant Litigation Group (4 Faneuil Hall Marketplace, 3rd Floor, Boston, Massachusetts 02109; Tel: 617-557-7177), *Silicone Breast Implants: A Briefing Paper*, undated.

Instability of Breast Implants. In spite of the knowledge of migration of silicone from injection sites, several companies manufactured and sold implants containing the same silicone fluids in a fragile silicone shell. The implants were unstable. The shells were susceptible to rupture, and they permitted diffusion of the silicone into the patients' bodies. One company identified the need for an alternative gel, but its efforts to develop such material were unsuccessful. Plastic surgeons commented on the instability of the implants and on silicone migration. Notwithstanding these complaints and the observation of biological activity of liquid silicones in pharmaceutical and insecticide application experiments jointly conducted by Dow Corning and Dow Chemical, the implant manufacturers held their position that silicone was biologically inert and safe for implantation in humans.

Local Complications. In many women, the capsule that formed normally around the breast implant showed tightening and contraction to cause severe pain, unnatural firmness, deformity, and chronic inflammation. Implant ruptures (with rates in excess of 50 percent), severe silicone bleeding (in an additional 20 percent of the cases), and the recommended removal of the ruptured implants and the uncontained gel (which may require multiple surgeries) result in local deformity and serious disfigurement.

Systemic Disease. The doctors who treat breast implant patients report cases of an atypical disease that differs from classical autoimmune diseases. This atypical disease is defined by a unique grouping of symptoms that include ocular, oral, and vaginal dryness; joint and muscle pains; cognitive dysfunction; chronic fatigue; and, in more serious cases, central nervous system impairment, kidney failure, and loss of bowel control. The doctors believe that the disease, which sometimes may not surface until six to ten years after implantation, results from a chronic immune response to the silicone in the implant and its degradation products, including silica. Causal evidence for connecting the disease with silicone is presented in the animal studies showing chronic arthritis induced by silicone, epidemiological studies showing elevated antibodies in women with breast implants, and a few publications in the scientific literature.

Manufacturer's Actions. Dow Corning has attempted to use "grass roots" organizations to disprove allegations of cover-up, destruction of documents detailing the need for a study of the safety of implants, and charges that the company reluctantly funded external scientific studies only after consulting with legal counsel to determine the impact on breast implant litigation.

Societal Cost. Notwithstanding Dow Corning's filing for protection under Chapter 11 bankruptcy, the company's financial performance has remained

strong and no job losses have occurred. In contrast, the implant patients are imposing tremendous costs on society. A number of health insurers, including the U. S. Government, have sought to assert their claimed subrogation rights. Although the exact amount claimed is unavailable because of the inability of the carriers to confirm the identity of women pursuing claims, an estimated 85 percent of the nation's health insurance carriers have attempted to seek reimbursement amounting to hundreds of million of dollars.

Hydrocephalus Shunt Implants

The hydrocephalus patients provide yet another important and quite different perspective of the biomaterials availability problem. The following summarizes the information provided by the Hydrocephalus Research Foundation.[77]

The Abnormality and Its Effects. Hydrocephalus refers to an abnormal accumulation of cerebrospinal fluid (CSF) within the cranial cavity and the accompanying increase in intracranial pressure. The condition is most commonly caused by some obstruction in the CSF flow passage ("noncommunicating") or may be a result of an imbalance between the production and the absorption of CSF ("communicating"). Congenital hydrocephalus may have its origin in intrauterine infection, perinatal hemorrhage, cyst or other such defect in the brain, or ventricular malformation. The acquired form, which develops after birth, may result from intraventricular hemorrhage, head injury, brain tumors, or certain diseases such as meningitis. In infants, hydrocephalus dilates the cerebral ventricles, causing an expansion of the skull (especially the forehead), downward deviation of the eyes, and compression of the brain. In older children and adults, the symptoms may include severe nausea and vomiting, migraine-like headaches, seizures, impaired vision, and inability to function normally. The best available statistics on the incidence of hyrocephalus suggests an occurrence rate of between 0.5 and 1.5 cases per 1,000 live births, but this grossly underestimates the size and scope of the patient population since it does not account for cases of acquired hydrocephalus at all ages. The prognoses for these patients are difficult to predict, but there is some correlation between the origin of the hydrocephalus and the outcome. Despite the variability of outcome, more and more of the properly diagnosed and treated infant and young patients can lead relatively normal lives. Untreated patients face progressive retardation, blindness, paralysis, and death.

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[77]Liakos, A. M., The Hydrocephalus Research Foundation, Inc., 1670 Green Oak Circle, Lawrenceville, Georgia 30243.

The Hydrocephalus Shunt. The most widely used current approach to the management of hydrocephalus involves the surgical implantation of a long, flexible, and sturdy tube—a shunt—that drains the excess CSF from the cranial cavity at the proximal end to the peritoneal cavity at the distal end. Whenever possible, sufficient length of catheter is placed to accommodate the physical growth of the patient. For some patients, however, extensions of the catheter are necessary during periods of rapid growth. Experiments conducted over the years with a variety of materials including silicone, polyethylene, polyvinyl chloride, Teflon® PTFE, rubber, and stainless steel have led to the conclusion that silicone is the best available material for the shunt. That conclusion remains the consensus today in spite of the controversies surrounding the biocompatibility of silicone materials generated by the breast implant–related events.

Patients' Appeal to Society. Hydrocephalus shunts save lives. The survival of the affected individuals depends on the immediate availability of the shunts for initial implants or replacement. All commercially available hydrocephalus shunts are manufactured from silicone. No suitable alternative material presently exists, nor is a promising substitute on the horizon. It is unfair to place the lives of the patients in jeopardy as they wait for the scientific community to develop new materials and shunts or for the legal system to decide on the course of an action to ensure the availability of silicone. Ongoing research ensures that silicone is essentially benign in the human body. In fact, silicone is used as a reference standard for testing the proposed alternative materials. These findings support the experience of the hydrocephalus patient population and the beliefs of the neurological community.

The current uncertainty in the supply of silicone materials for implant application is therefore tantamount to a serious impending crisis for the community. Accordingly, patients question society's wisdom—or the lack of it—in indiscriminately allowing a public policy with far-reaching consequences to be dictated by special-interest groups. Speculation about the risk of using silicone in the manufacture of implantable devices should be balanced with what is known about the risk to patients should they be unable to gain access to the silicone-based systems. Patients who depend on the shunts have no alternatives. The risk in denying access to the only viable material of which the shunts are made, they note, is death. In that context, they support the Biomaterials Access Assurance Act, but, in doing so, they are not insensitive to the plight of the patients injured by other devices or to the original purpose of the legal system. They recognize the complexity of the issue and endorse "an opportunity to bring together basic scientists, engineers, clinicians, policymakers, patients, and patient

advocates in support of an environment fostering advances in our ability to improve treatments and outcomes—an environment in which concerns about safety and effectiveness (or efficacy) are balanced with availability."[78]

These descriptions show that patients have diverse experiences and opinions concerning the role of the liability system and the responsibilities and actions of the biomaterials and the medical-device manufacturers, the regulatory agency, and the medical and legal communities. These experiences and opinions do not add up to a single patient perspective. It is evident, however, that the patient groups commonly support the development of biomaterials with long-term biocompatibility; ask to be included early in the development process; and request that the manufacturers, medical professionals, and regulators be sensitive to their concerns, inform them fully of the risks and benefits, and understand their plight when errors occur. They note the interdependence between the different communities and stress the need for cooperation. One patient group puts it succinctly: "Without you, we have no hope for a better future; without us, you have no job."[79]

A key feature of the patients' situation is its diversity. Patients include persons who may be harmed by the same decision that brings compensation or justice to others. This underscores the challenge faced by the courts in making optimal decisions that require a wide appreciation of the often difficult-to-foresee consequences of their judgments.

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[78] Liakos, A. M., The Hydrocephalus Research Foundation, Inc., 1670 Green Oak Circle, Lawrenceville, Georgia 30243.

[79] Cowley (1994).

6. Potential Effects of a Biomaterials Shortage

A shortage of biomaterials for medical applications seems likely to affect the companies that use biomaterials to manufacture devices, the industry at large, and, most important, the health of the people of the United States.

Companies. Medical-device firms confronting a shortage of biomaterials may have to stockpile materials, shift resources from product innovation and development to finding and qualifying alternative suppliers, confine their operations to offshore sites, abandon certain products, or leave the business entirely. An industry survey and the Aronoff study indicate that the device manufacturers have reacted to the situation by costly and temporary measures such as stockpiling and seeking alternative suppliers—especially from Europe and Japan—although companies from those countries are also showing reluctance to supply materials, even under indemnification agreements.[80]

However, these actions do not provide long-term solutions. The problems with these remedial measures include questions about whether the physical properties of stockpiled materials remain stable over the long term, uncertainties about finding proper substitutes for discontinued materials and the costs of the substitutes, time and resources required for finding the substitutes and obtaining regulatory approvals, the continued possibility of being subjected to liability, and questionable sustainability of supply.

Industry. In 1993, the medical-device industry in the United States employed 282,000 people and had revenues of $43 billion, representing 46 percent of the global output.[81] Its exports, which have been growing at a 16 percent annual rate since 1988, contributed to a $5 billion trade surplus in 1994.[82] The industry invests heavily in R&D—about 6.8 percent of sales—which far exceeds the all-industry average of approximately 3.8 percent.[83]

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[80] The Wilkerson Group (1995); Aronoff Associates (1994).

[81] The Wilkerson Group (1995), pp. 26–28.

[82] HIMA (1995c).

[83] The Wilkerson Group (1995), pp. 29–30.

The Aronoff study forecasts that within three years some of the biomaterials, the products made from them, and the medical procedures employing them may become unavailable, forcing a compromise in both public health and the world leadership of the United States in the implantable medical-device industry. As noted earlier in this paper, future prospects for medical devices hinge to a large extent on the many prospective advancements at academic research centers and small entrepreneurial start-up companies in fields such as tissue engineering and cell therapy. Much of this innovation has significant potential for commercialization. But realizing that potential may require support and cooperation from companies with expertise in material sciences, which is unlikely in the current situation.

A more subtle effect on the industry could also occur. Many device manufacturers have benefited from materials developed for other than medical applications. The companies that developed these materials represent repositories of expertise in materials manufacture. In some instances, the decision to restrict or discontinue the supply of specific materials has indirectly brought with it the loss of support and cooperation that the device companies have traditionally received from the materials suppliers and associated industries with well-established materials research, development, and manufacturing infrastructure.[84] Such cooperation is particularly important to small medical-device companies, which by themselves are usually not equipped to investigate thoroughly all the critical materials properties (as opposed to biocompatability), establish specifications, and ensure quality and reproducibility.[85]

Health Care. A shortage of biomaterials could have a broad impact on health care for U.S. citizens. In the near term, HIMA and the Biomaterials Availability Coalition[86] estimate that a shortage could affect about 85 products and 30 surgical procedures. These products and procedures involve an estimated 7.4 million patients. The most immediate and noticeable effect may be that implantable medical devices for patients become less available. During the past fifteen years, the most active areas of new implantable prosthetic products have included cardiovascular technologies such as pacemakers, defibrillators, artificial heart valves, and cardiac assist devices; artificial joints; skin substitutes; drug infusion systems; and cochlear implants[87]—all using biomaterials of various

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[84] The Wilkerson Group (1995), p. 113.

[85] Ward (1995).

[86] HIMA (1994a); Biomaterials Availability Coalition (1994a).

[87] National Heart, Lung and Blood Institute (1995).

kinds. Other affected products include implants such as hydrocephalus shunts, orthopedic prostheses, and intraocular lenses. Approximately 160 new products were introduced during this period by 74 companies, 61 of which are based in the United States. The uncertainty over biomaterials availability is expected to affect these companies' ability to continue manufacturing these products.

How prevalent is the shortage? Precise effects are difficult to measure, but the Wilkerson Group survey[88] found that 41 percent of 526 respondent medical-device manufacturers reported having difficulty obtaining materials currently, and another 9 percent expected difficulty within 2 years; the corresponding figures for implantable product manufacturers were 73 percent and 13 percent, respectively. According to the FDA, a scarcity of critical products has not yet occurred, but the agency has expressed concern about potential shortages.[89] And medical professional societies such as the Society for the Advancement of Women's Health Research and the American Heart Association have also expressed concerns about the biomaterials supply situation.[90]

Over the longer term, innovation in the medical-device field could suffer. Academic and entrepreneurial institutions are unlikely to be able to conduct their research on new diagnostic and therapeutic approaches involving such technologies as tissue engineering and cell therapy and transform them into viable products, because most of these efforts require the use of biomaterials. This could potentially retard innovation in this field.

The Effect on Innovation. Opinion is divided about the effect of the legal and economic climate on innovation. On the one hand, some argue that "even very substantial liability risks may be insufficient to deter investments in developing products that are viewed as potential blockbusters"[91] and, in very broad terms, that "except in very high levels of liability, the net effect of product liability is to foster innovation rather than deter it."[92] Such arguments find support in a 1987 survey of risk managers of 232 large U.S. corporations,[93] which found that "the pressures of product liability have hardly affected larger economic issues" and that the impact of the legal system has been to make the products safer, improve manufacturing procedures and labels, and make instructions for use more explicit.

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88 The Wilkerson Group (1995), p 108.

89 Nemecek (1996).

90 Greenberger (1995); Oparil (1995).

91 Garber (1993), p. 165.

92 Viscusi (1991).

93 Ide (1994).

On the other hand, a 1988 survey of 500 chief executive officers reached the opposite conclusion.[94] Given that innovation is not a choice but an imperative for the device industry, the question is not whether the legal environment discourages innovation and where investments for innovation are made, but what types of innovation are discouraged and what investment decisions should be made in response.[95] This issue forces scientists, engineers, physicians, and manufacturers to make trade-offs between risks and benefits at a very early stage in the product-development process, all the while being aware that every medical innovation has some potential for causing injury despite the most conscientious effort, and that zero risk is not achievable. Commentators[96] observe that this process may complicate litigation, particularly when nontechnical personnel, judges, and juries are asked to interpret and make decisions based on highly technical documentation of these trade-offs.

Although the effects on innovation can be debated, DuPont, which has always remained in the forefront of innovation in chemical and material sciences, will not commit R&D resources for any new business ideas or concepts involving synthetic materials for use in implantable medical devices. According to MacLachlan,[97] "since DuPont cannot limit or justify the risk, either through regulatory standards or reasonable potential financial liability, it will not work in these areas and will forbid use of DuPont materials or expertise to be applied in these areas." Other major materials source companies have indicated similar intentions. This, he continues, "is extremely discouraging and frustrating for scientists in a corporation with the technical capability to make all kinds of new materials."

The decisions by DuPont, Dow Chemical, Dow Corning, and others to restrict or discontinue supply of materials for implantable devices seem likely to have two effects on device innovation. First, the decisions will force the device manufacturers to divert resources from research and development of technologies and products to search for, secure, and qualify equivalent materials.[98] The diversions may sometimes be substantial. For example, Ethicon, Inc. of Somerville, N. J., a leading suture manufacturer, spent 18 months finding and testing a polyethylene material to replace the one being withdrawn by DuPont.[99] The time and resources expended in such efforts to simply

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[94] Hunziker and Jones (1994).

[95] Garber (1993), p. 144; Epstein (1987).

[96] Morrow (1994); Epstein (1987).

[97] MacLachlan (1994).

[98] Biomaterial Availability Coalition (1994); HIMA (1995d).

[99] Service (1994).

recapture current capabilities may come at the expense of new innovative approaches to health care. This is because the same, often limited, scientific expertise is required for both finding replacements for the materials used in existing devices and applications, and for developing better applications with existing, qualified materials.

Second, the suppliers' decision to withdraw from the market may cause some projects to be abandoned altogether. Two projects—a small implantable blood pump at Nimbus, a California-based development stage company, and a pacemaker at Medtronic, a Minneapolis-based leading cardiovascular device company—provide examples of these effects.[100] When the Nimbus blood pump project was halted because of DuPont's decision to phase out a material component, the company searched several months for an alternative material, only to find that DuPont had subsequently acquired the rights to the new material, putting the company back into the search. (DuPont did not know of the Nimbus project, neither Nimbus nor any other company had never discussed this matter with DuPont, and DuPont's acquisition was in no way connected with any implantable device application.[101]) Medtronic abandoned work on promising new insulation materials for pacemaker wires when the respective suppliers decided to withdraw from sale for use in medical implants.

There is also less chance of a breakthrough that leads to new devices for addressing as yet unmet medical needs. The vast R&D resources of the exiting companies (i.e., DuPont, Dow, Dow Corning) have greater potential for generating important advances in materials science than do the smaller laboratories of the alternative materials suppliers.

Discussion at the 1995 NIH workshop on "Biomaterials and Medical Implant Science: Present and Future Perspectives" noted that the need for access to materials, research on materials, and expansion of platform knowledge on materials to ensure continued innovation and availability of medical devices is not well served by the current legal atmosphere.[102] A speaker from a tissue engineering technology company noted that its efforts to develop new treatments for burn victims were affected by the restricted availability of biomaterials. As a result, it uses "what is available, not what is best for the patient. Small companies without the deep pockets to protect suppliers from liability claims cannot find medical manufacturers to make new materials."[103]

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[100] The Wilkerson Group (1995), p 113; Service (1994).

[101] Schmucki, R. F., DuPont, *Unpublished Communication*, 1996.

[102] Citron (1995).

[103] G. Naughton, quoted in "Speakers Highlight Importance of Biomaterials Research" (1995).

The stringent indemnification demands imposed on the device industry by the current biomaterials supply situation favor larger device companies, which can better afford the necessary guarantees.[104] This puts start-up device companies and entrepreneurs at a disadvantage because of their limited financial resources. The imbalance may shift the nature of innovation in the direction of incremental advancements as generally practiced by the larger companies, which tend to be risk averse.

Finally, the supplier issues potentially extend beyond biomaterials to include electronic circuits, batteries, and other increasingly important components of implantable devices. All told, these consequences could have substantial adverse effects on patient care in the United States.

Our analysis, in this section and others, is based on an extensive review of the literature in the field—medical, business-related, and legal—as well as interviews with decisionmakers and scientists in the biomaterials and medical-device industries. It should be noted that much of the information about the availability of materials and the actions of biomaterials suppliers comes from those same interested parties. An independent verification has not been undertaken by RAND or others. However, we have attempted to ensure that we used the most reliable and verifiable sources from this community. We also note that with the passage and signing of the 1998 Biomaterials Access Assurance Act, the Congress and the President, who have very different views on product liability legislation, have agreed that such legislation was necessary in light of possible constraints on the availability of biomaterials.

Despite this caveat, this section should give a clear picture of the potential costs to society of the withdrawal of biomaterials suppliers from the market. The complex system of researchers, suppliers, manufacturers, health care providers, and patients outlined here also underscores why we have put forth the hypothesis that courts often may not have access to all the relevant information about the social costs of their decisions.

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[104] Baker (1995).

7. Concluding Thoughts

Balancing the interests of the various parties in the biomaterials debate—injured patients, benefited patients, manufacturers, and researchers—and considering potential benefits and risks to future patients that may come from research (or the lack thereof) is complex. If the policy approach we use in striking this balance does not appropriately regard the interests of all parties, including current and future patients who could benefit from implantable devices, the overall benefit to the public could be lessened. Patients can find their quality of life, and in some instances life itself, threatened. Future patients may be denied innovative solutions to medical problems that our major research investments could provide. And the viability of a small but important sector of the nation's economy may be threatened.

Although we are not able to draw strong conclusions about whether a biomaterials shortage affects the welfare of current patients and constrains the prospects of future medical innovation, our analysis suggests that the benefits to current and future patients of even less-than-perfect uses of biomaterials are undervalued in current court proceedings. The hypothesis advanced here is that the tort system often does not adequately value the overall benefits to the public of biomaterials use. If this hypothesis proves correct, important implications for policy and legislation immediately follow.

Court cases, which by their nature settle disputes between only a few of the many parties involved, often cannot adequately take into account the overall benefits of biomaterials products. This analysis has shown that even though the applications of some biomaterials result in undesirable outcomes for some patients, there are positive benefits for other patients that may be even more beneficial to society. This poses a dilemma: Choices that prevent undesirable uses of biomaterials may also preclude desirable uses.

Biomaterials suppliers are not insensitive to the societal value of the use of their materials in products that enhance or save lives. But if they perceive that the economic risk from this small part of their overall business is too great, it will outweigh other considerations in their decisions. Our analysis suggests that this largely results in the dilemma posed above. In the absence of other policy mechanisms besides the tort system, the opportunity to find the best balance of benefits for all the parties involved may be constrained.

In July 1998, Congress enacted the Biomaterials Access Assurance Act in response to this evolving situation. The act's intent was to ensure biomaterials access for device manufacturers and those who develop implantable devices. The act affords biomaterials suppliers some shelter from liability lawsuits if they simply act as suppliers of the raw biomaterial for medical devices and the material meets quality standards. Although our examination does not provide strong enough evidence to conclude that the availability of biomaterials has adversely affected patient care and future innovation, the information we have collected suggests that the issue is important. Given this, a careful, fact-based examination of the evolving situation and a careful assessment of whether the legislation is having its intended effect are both warranted.

Appendix: List of Discussants

This paper has been made possible by inputs from and discussions with a number of individuals from a broad range of institutions. The following list identifies those to whom copies of early drafts, in part or in full, were sent during the course of developing the paper. Those providing significant contributions have been listed in the acknowledgments; among the others on the list, some have offered useful criticisms, suggestions, and advice.

Academic Institutions

Robert Langer, Sc.D.
Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering
Massachusetts Institute of Technology
77 Massachusetts Ave., E25-342
Cambridge, MA 02139

Pierre M. Galletti, M.D., Ph.D.
Professor of Medicine
Division of Biology and Medicine
Brown University
Box G-B
Providence, RI 02912

Jeffrey A. Hubbell, Ph.D.
Professor of Chemical Engineering
California Institute of Technology
Division of Chemical & Chemical Engineering, 210-41
Pasadena, CA 91125

James M. Anderson, M.D., Ph.D.
Institute of Pathology
Case Western Reserve University School of Medicine
University Hospitals of Cleveland
2085 Adelbert Rd.
Cleveland, OH 44106

Robert M. Nerem, Ph.D.
Director
Institute for Bioengineering and Bioscience
Georgia Institute of Technology
281 Ferst Drive, N.W.
Atlanta, GA 30332-0363

Robert C. Eberhart, Ph.D.
Professor and Chair of Biomedical Engineering
Southwestern Medical Center
University of Texas
5323 Harry Hines Boulevard, Room G8-248
Dallas, TX 75235-9130

Robert E. Baier, Ph.D.
HealthCare Instruments and Devices Institute
State University of New York at Buffalo
105 Parker Hall
Buffalo, NY 14214

Joachim Kohn, Ph.D.
Professor
Department of Chemistry
Wright and Rieman Laboratory
Rutgers University
Taylor Road
Piscataway, NJ 08855-0939

Peter Eisenberger, Ph.D.
Director, Princeton Materials Institute
Department of Physics, Bowen Hall
Princeton University,
Princeton, NJ 08540

Dianne Rekow, Ph.D., D.D.S.
Chair
Department of Orthodontics
University of Medicine and Dentistry
110 Bergen Street
Newark, NJ 07013

Peter Katona, Sc.D.
The Whitaker Foundation
1700 North Moore Street
Suite 2200
Rosslyn, VA 22209

Buddy Ratner, Ph.D.
NESACIBIO
University of Washington, BF-10
Seattle, WA 98195

Government Agencies (NIH, NSF, FDA, DoD)

John T. Watson, Ph.D.
Head
Bioengineering Research Group
National Heart, Lung, and Blood Institute
National Institutes of Health
Two Rockledge Center, Suite 9044
6701 Rockledge Drive, MSC 7940
Bethesda, MD 20892-7940

Col. Bill Wiesmann, M.D.
HQ USA
Medical Research Material Command
Ft. Detrick, MD 21702

Janie Fouke, Ph.D.
National Science Foundation
4201 Wilson Blvd.
Room 565
Arlington, VA 22230

Paul Didisheim, M.D.
Head
Biomaterials Program
Bioengineering Research Group
National Lung, Heart, and Blood Institute
National Institutes of Health
Two Rockledge Center, Suite 9044
6701 Rockledge Drive, MSC 7940
Bethesda, MD 20892-7940

Sheila Newton, Ph.D.
Office of the Director
National Institute of Environmental Health Sciences
Physical Sciences Laboratory
Bldg. 31, Rm. BlCO2
Bethesda, MD 20892

Elliot Postow, Ph.D.
Chief of the Special Review Section
Division of Research Grants
Referral and Review Branch
National Institutes of Health
Two Rockledge Center
6701 Rockledge Drive, MSC 7852
Bethesda, MD 20892-7852

Danuta M. Krotoski, Ph.D.
Chief
Basic Rehabilitation Medicine Research Branch
National Center for Medical Rehabilitation Research
National Institute of Child Health and Human Development
National Institutes of Health
Building 616, Room 2AO3
6100 Executive Boulevard
Rockville, MD 20814

Lore'Anne McNicol, Ph.D.
Director
Division of Extramural Activities
National Eye Institute
National Institutes of Health
Executive Plaza South, Room 350
6120 Executive Plaza Boulevard, MSC 7164
Rockville, MD 20852-7164

Robert L. Strausberg, Ph.D.
Chief
Sequencing Technology Branch
National Center for Human Genome Research
National Institutes of Health
Building 38A, Room 604
38 Library Drive, MSC 6050
Bethesda, MD 20892-6050

Michael F. Huerta, Ph.D.
Associate Director for Scientific Technology and Resources
Division of Neuroscience and Behavioral Science
National Institute of Mental Health
National Institutes of Health
Parklawn Building, Room 11-103
5600 Fisher Lane
Rockville, MD 20857

Norman Braveman, Ph.D.
Assistant Director for Program Development
National Institute of Dental Research
National Institutes of Health
Natcher Building, Room 4AN-24D
Bethesda, MD 20892

Carolyn Holloway, Ph.D.
Acting Director
Bioresearch Technology Program
National Center for Research Resources
National Institutes of Health
One Rockledge Center, Suite 6160
6705 Rockledge Drive
Bethesda, MD 20892-7965

Donald E. Marlowe, M.S.
Acting Director
Office of Science and Technology
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard, HFZ-100
Rockville, MD 20850

Edward Mueller
Food and Drug Administration
12200 Wilkins Avenue
Rockville, MD 20852

Lyn Yaffee, Ph.D.
Naval Medical Research and Development Command
8901 Wisconsin Avenue
Bldg. 1T-12
Bethesda, MD 20899

Joseph Osterman, Ph.D.
3080 Defense Pentagon
Room 3D129
Washington, DC 20301-3080

Patients, Patient Advocates, and Consumer Interest Groups

Terrie Cowley
President and Cofounder
The TMJ Association, Ltd.
6418 West Washington Blvd.
Milwaukee, WI 53213

Ann Marie Liakos
1670 Green Oak Circle
Lawrenceville, GA 30243

Peggy Phillips, Esq.
Federal Emergency Management Agency
500 C Street, S.W.
Washington, DC 20472

Sidney M. Wolfe, M.D.
Public Citizen Health Research Group
1600 20th Street, N.W.
Washington, DC 20009

Joe Belluck
Staff Attorney
Public Citizen—Congress Watch
215 Pennsylvania Avenue, S.E.
Washington, DC 20003

Michael R. Hugo
Co-Chair
ATIA Breast Implant Litigation Group
4 Faneuil Hall Marketplace
3rd Floor
Boston, MA 02109

Sandra Finestone
Women's Implant Information Network
Finestone & Finestone
1759 Harvard Avenue
Irvine, CA 92714

Sharon Green
Y-Me National Breast Cancer Organization
National Headquarters
212 W. Van Buren St., 4th Floor
Chicago, IL 60607-3908

Audrey Straight
AARP
601 E Street, N.W.
Washington, DC 20049

Heather Bev Lever
Health Economic Development, Ontario
56 Wellesley Street, West 3rd Floor
Toronto, Ontario M5S2S3
Canada

Professional Societies and Trade Associations

Kevin O'Connor
Executive Director
AIMBE
200 G Street, N.W.
Suite 800
Washington, DC 20005

James Benson
Executive Vice President for Technology and Regulatory Affairs
Health Industry Manufacturers Association
1200 G Street, N.W., Suite 400
Washington, DC 20005

Bernard Leibler, M.A.
Director
Technology and Regulatory Affairs Department
Health Industry Manufacturers Association
1200 G Street, N.W., Suite 400
Washington, DC 20005

Jeffrey J. Kimbell
Medical Device Manufacturers Association
1575 Eye Street, N.W.
Suite 500
Washington, DC 20005

Legal Professionals

Richard A. Merrill, L.L.B.
Daniel Caplin Professor of Law
University of Virginia School of Law
Charlottesville, VA 22901

Vincent Brannigan, Ph.D.
Department of Fire Protection Engineering
Room 0151, Engineering Classroom Building
A. James Clark School of Engineering
Glenn L. Martin Institute of Technology
University of Maryland
College Park, MD 20742-3031

Raw Materials Suppliers and Medical Device Manufacturing Companies

Ross Schmucki
Senior Counsel
DuPont
Legal D7082
1007 Market Street
Wilmington, DE 19898

Katherine Knox
Business Program Manager
DuPont Central Research & Development
Building 326, Room 210
P.O. Box 80326
Wilmington, DE 19880-0326

Stephanie Burns
Manager: FDA and Women's Health Issues
Dow Corning Corporation
Midland, MI 48686-0994

Paul Citron
Vice President, Science and Technology
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, MN 55432

John H. Lapke
Senior Counsel
Cardiac Pacemakers, Inc.
Guidant Corporation
4100 Hamline Ave., North
St. Paul, MN 55112-5798

John D. Paulson, Ph.D.
Vice President, Regulatory Affairs
Ethicon, Inc.
P.O. Box 151
Somerville, NJ 08876-0151

Tom Hughes
Medical Alley Association
Travelers Express Tower, Suite 725
1550 Utica Avenue South
Minneapolis, MN 55416

Dane Miller, Ph.D.
President and CEO
Biomet, Inc.
Airport Industrial Park
P.O. Box 587
Warsaw, IN 46580

Thomas M. Loarie
Chairman and CEO
Keravision
48630 Milmont Drive
Fremont, CA 94538-7353

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